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Presidential Address: The Genetics of Human Behavior—Lessons for Two Societies[1]

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Introduction

Previous presenters of this address have tended to examine issues relevant to one of two socieites—our own, i.e., The American Society of Human Genetics, or society in general. I want to discuss the subject of the genetics of human behavior and its implications for both of these societies.

Initially, the thought of presenting this subject gave me a few tinges of trepidation, given the nightmare that befell one of our members when he entered into this territory over 10 years go. That generated a previous presidential address in his defense, by Dr. John Hamerton, in 1975 (Hamerton 1976). However, in the present era, where genes for Huntington disease, Alzheimer disease, manic-depressive disorder, X-linked mental retardation, schizophrenia, and others have been physically localized on the human chromosome map, it is apparent that the public expects us to do more, not less, in the field of understanding the function of our most complex organ—the brain.

When I applied to medical school, several centuries ago, I was asked the inevitable question: "Why do you want to become a doctor?" I replied: "Because that is the one field that brings together two of my major interests, biology and psychology." I have spent the first 20 years of my career on the biology part, but things have finally come full circle and in the past 8 years the psychology half has been catching up. As my psychologist wife said: "She pulled me kicking and screaming out of the lab and into the clinic." To my amazement I found there an intellectually, scientifically, and emotionally satisfying challenge—a genetic disorder that could not be better suited for the study of the genetics of behavior if I had dreamed it up myself. It is as though, with a jerk of the head, a blink of the eye, or utterance of a grunt, those affected with Tourette syndrome (TS) are saying: "I have this gene—come study me." So I did.

The thoughts I bring to you are based on over 8 years of intense clinical involvement with this group of remarkable children and adults and their relatives. When Brenda and I first became involved in studying this disorder, we thought it was an extraordinary rare disease of the type that is of interest mostly to medical geneticists. At that time I was spending only one afternoon a week in the clinic, with an assortment of hereditary neurological disorders. The TS patients came in slowly at first, one or two a month. After our first public discussion of the syndrome on television, a rising tide quickly became a flood, one a week, two a week, then four a week, and now, for the past 2 years, 8–12 a week. We were astounded this disorder was so common. The numbers mounted, 250, then 500, and now over 1,200 plus 500 with related disorders. Each family received the kind of compulsive pedigree taking that only a dyed-in-the-wool geneticist can do and the kind of emotional probing that a clinical psychologist can add. The ideas I will present to you have yet to be put to the ultimate yardstick of the geneticist—the mutation-specific oligonucleotide probe. At this stage they are culled from that time-honored gold mine called clinical experience.

A Common Disorder

The first message, which has implications for both societies, is that TS is a common disorder. As physicians have become more familiar with the syndrome, the number of diagnosed cases has increased (table 1). Two recent studies on the epidemiology of TS, based on questionnaires sent to physicians and public announcements, have suggested a frequency in male children of 1/1,000–1/1,500 (Burd et al. 1986*a*, 1986*b*; Caine et al. 1988). Although motor and vocal tics have

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1. The contents of this article represent the opinion of the author and have not been peer reviewed.

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Table 1

How Common Is TS?

Type of Study	Frequency in Males	Reference
Review of records Mayo clinic 1968–79	1/100,000	Lucas et al. 1982
Questionnaire to physicians in North Dakota (children)	1/1,000	Burd et al. 1986*b*
Questionnaire and public announcements, Monroe County, NY	1/1,500	Caine et al. 1988
On-site monitoring of one school district for 2 years	1/100	Comings et al., submitted

to be present almost daily for a year, the symptoms are often suppressed in the doctor's office, and a careful longitudinal history is essential or the diagnosis may be missed. Because of this the questionnaire approach may underestimate the number of cases.

We have just completed a study in cooperation with a school psychologist thoroughly familiar with this disorder (Comings et al., submitted). Daily monitoring of three schools over a period of 2 years showed that in boys the frequency of definite, rigid-research-criteria TS was 1/100. These were not just children with benign tics. All had problems with varying combinations of attention-deficit disorder, compulsive behaviors, learning and reading disabilities, stuttering, and conduct disorders. The frequency is particularly high in children compared with adults because it is not unusual for the tics to slowly disappear with age.

A Semidominant Trait

Although we and others have previously visualized TS as a dominant disorder with a carrier frequency of approximately 1.2%, as we continued to take pedigree after pedigree it began to dawn on us they all made more sense if many TS cases were homozygous for the *Ts* gene. In fact, two of three of the previous TS segregation analyses, using POINTER, actually suggested a semidominant mode of inheritance (table 2). Table 3 lists all the reasons why I believe that more than half of the cases of TS that come to the clinic may be homozygous for the *Ts* gene.

If these two observations—a frequency of 1/100 in males and half of them being homozygous—are correct, then 13% of the population would carry the *Ts* gene. Combining possible errors in both estimates sug-

Table 2

Segregation Analysis in TS

Study	Penetrance		Carrier Frequency (%)	*Ts/Ts* (%)
	Ts/Ts	*Ts/ts*		
Semidominant:				
Comings et al. 1984:				
Males	.99	.68	1.2	
Females	.89	.30		
Overall	.94	.50		
Devor 1984:				
Males	.99	12.5	7.7	23.7
Females	.99	1.5		
Overall	.99	7.3		
Dominant:				
Pauls and Leckman 1986:				
Males	.99	.99	1.2	<1
Females	.71	.71		
Overall	.85	.85		

Table 3

Evidence That TS Is a Semidominant Trait

Segregation analysis (Comings et al. 1984; Devor 1984)
35% of pedigrees: associated behaviors (alcoholism, ADDH, panic attacks, or obsessive-compulsive behaviors) on both maternal and paternal sides
45% of pedigrees: tics or associated behaviors on both sides
Visual field studies of Enoch et al. (1988*a*, 1988*b*): show defects in both parents 70% of the time
>96% of pedigrees: propositus more severely affected than either parent
60% of pedigrees: neither parent showing motor or vocal tics
Serotonin and tryptophan significantly decreased in both parents

gests a carrier range of 5%–20%. The pedigrees suggest that during their lifetime about half of these carriers have some symptoms of the TS spectrum of disorders.

A Spectrum Disorder

Evidence that TS is associated with a wide spectrum of attentional, perceptual, learning, compulsive, anxiety, and mood disorders has been previously presented and debated in the *Journal* and will not be repeated here. However, for those who may still doubt that it is a generalized behavioral disorder, I would like to call attention to a remarkable book by Oliver Sacks called *Awakenings* (Sacks 1983). He describes in eloquent detail the effect of L-dopa treatment of patients with postencephalatic Parkinson disease who have spent their lives as sleeping Rip Van Winkles. Their dopamine-depleted brains are hypersensitive to the effects of the drug and provide a remarkable model of drug-induced TS. In addition to vigorous motor, vocal, and complex tics, all of the rest of the wide range of associated spectrum behaviors we and others have observed come bursting forth geyserlike from this perfect chemical experiment of nature (table 4). Depending on the dose of L-dopa the symptoms could be produced and eliminated as easily as turning the volume knob on a stereo.

While this emphasizes the role of dopamine hypersensitivity in the symptom complex of TS, studies of blood serotonin and tryptophan (Comings and Comings 1988, and in press) suggest that the primary genetic defect may be in serotonin. As described in detail elsewhere, a serotonin defect is consistent with the entire behavioral spectrum in TS and with dopamine hypersensitivity (Comings, submitted).

Alcoholism, Obesity, and TS

Obsessive-compulsive behaviors are universally accepted as part of the TS spectrum. One of the associated compulsive behaviors not listed above that we have repeatedly observed in TS pedigrees is the increased frequency of alcoholism and drug abuse. To determine whether this was simply our imagination or was real, I counted the number of first-, second-, and third-degree relatives with either life-interfering problems with alcoholism and or drug abuse in the previous 20 TS pedigrees and compared them with the next 13 prenatal diagnosis pedigrees taken, asking the identical questions. The results are shown in figure 1.

In the previous 20 TS families 18.7% of the 214 relatives had problems with alcoholism and/or drug abuse, compared with 4.2% of the 188 members of 13 control families ($P = <.00001$). If one of the control families where a member had TS and two control families where a member had attention-deficit disorder were removed,

Table 4

Spectrum of Behaviors Seen after Treatment of Parkinson Disease with L-Dopa

Aggressive
Agitated
Angry
Complex tics
Compulsive behaviors
Compulsive eating
Compulsive masturbation
Demanding
Driven behaviors
Echolalia
Hearing voices
Hyperactive
Hypersexual
Impatient
Insomnia
Mania
Motor tics
Nightmares
Obsessive thoughts
Palilalia
Perseveration
Pressure of speech
Polydispia
Rages
Stereotyped behaviors
Vocal tics

NOTE.—The diagnostic characteristics of TS are in italics. The behaviors seen in both L-dopa-treated Parkinson disease and TS are in roman type.

SOURCE.—Sacks (1983).

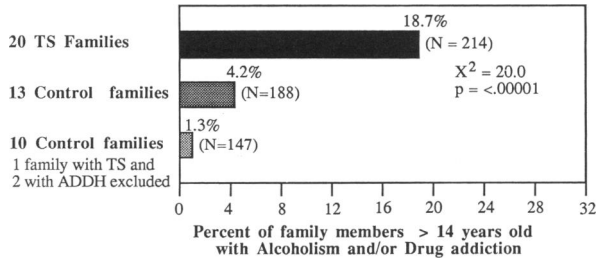

Figure 1

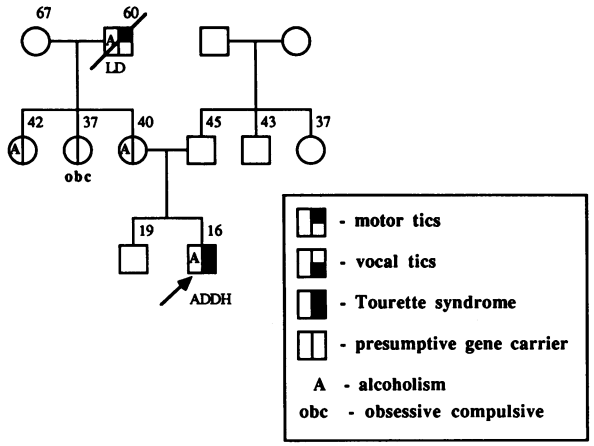

Figure 3

then the frequency of alcoholism and/or drug abuse dropped to 1.3%.

To show that these problems were clustered in some families and were totally absent in others, figure 2 illustrates the distribution of the number of TS-affected individuals per family who have alcoholism.

It can be seen that a significant percentage of the alcoholism in the TS group is accounted for by five families, each of which contains two to nine alcoholics, i.e., by familial alcoholism. In a more selected group of 50 TS families, (Nee et al. 1980) found a positive history of alcoholism in 52%.

Although different sets of families would produce a different percentage, we have observed this trend in the past 200 pedigrees, since the appropriate questions were asked. Figure 3 shows what we see so frequently. (We have since studied 1,843 relatives over 14 years of age in 130 TS pedigrees and 390 relatives over 14 years of age in 25 control families. Severe problems with alcoholism or drug abuse were present in 14.45% of the TS relatives versus 4.36% of the control relatives [$P <$ .0005). Obesity consisting of being 100 pounds or more overweight was present in 3.17% of all TS relatives versus 0.77% of control relatives [P = .01].)

Here the propositus is a 16-year-old TS male who has already been in a residential treatment facility for over a year for alcohol and drug abuse that started at age 14 years. His mother was an alcoholic, and her father had chronic motor-tic disorder and a life long history of alcoholism. The maternal aunt was also an alcoholic. Here the presence of TS in her son and chronic motor tics in her father suggest the mother was a *Ts* gene carrier in whom the *Ts* gene was being expressed only as alcoholism. One lesson is that, when taking pedigrees of alcoholic families, it is not adequate to just ask about chronic motor or vocal tics in the patients themselves; other members of the family who may not even be alcoholic must also be interviewed. As shown in figure 4, alcoholism is not infrequently present on both parental sides.

Cloninger and colleagues (Cloninger et al. 1981, 1986; Cloninger 1987; Gilligan et al. 1987) have divided alcoholism into type I (minimally hereditary, female predominant) and type II (strongly hereditary, male predominant). I have been repeatedly struck by the similarities between the psychological profile of type II alcoholics and that of many individuals with TS, especially those with attention-deficit hyperactivity disor-

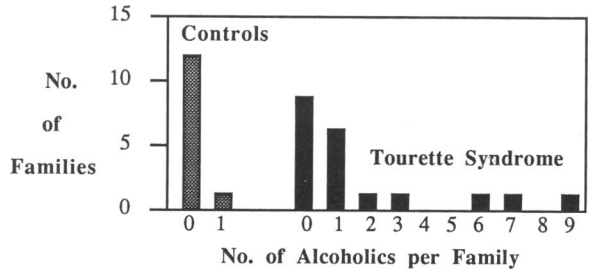

Figure 2

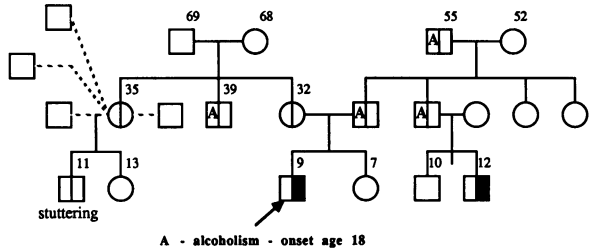

Figure 4

Table 5

Comparison of Two Types of Alcoholism and TS

Features	Type I Alcoholism	Type II Alcoholism	TS
General personality	Passive/dependent	Impulsive/compulsive	Impulsive/compulsive
Alcohol-related problems:			
Age at onset	After age 25 years	Before age 25 years	Before age 25 years
Ability to abstain	Good	Poor	Poor
Aggressive when drunk	Rare	Common	Common
Loss of control	Common	Rare	Rare
Guilt about alcohol use	Common	Rare	Rare
Personality traits:			
Sensation seeking	Low	High	High
Risk taking	Low	High	Often high
Reward dependence	High	Low	Low
Personality when abstinent	Worrying	Distractible	Distractible
	Anxious	Impuslive	Impulsive
	Apprehensive	Easily bored	Easily bored
Genetics:			
Sons	Alcoholic	Alcoholic	Alcoholic
Daughters	Alcoholic	Nonalcoholic	Obese

SOURCE.—Comings (submitted).

der (ADHD). These are shown in table 5 (Comings, submitted). Since there is much evidence pointing to a correlation between childhood ADHD and adult alcoholism (Morrison and Stewart 1971; Cantwell 1972; Blouin et al. 1978; Loney et al. 1981; Gittelmann et al. 1985), and since 50% of TS patients have ADHD, the increased frequency of alcohol problems we observe in TS relatives is not surprising.

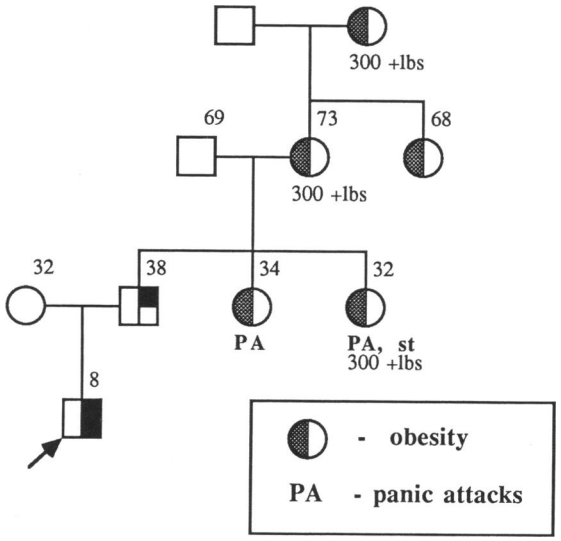

Figure 5

Type II alcoholism is so male predominant that some have even suggested that the gene for it is on the Y chromosome. Our observations in TS suggest an alternative explanation. When we ask female relatives of our TS patients whether they have any compulsive behaviors, a frequent answer is, "yes, eating." This response is often verified by visual inspection. Figure 5 illustrates the point.

The tendency for familial obesity to be limited to the female line has been reported in adoption studies of obesity (Price 1987; Price et al. 1987). As illustrated

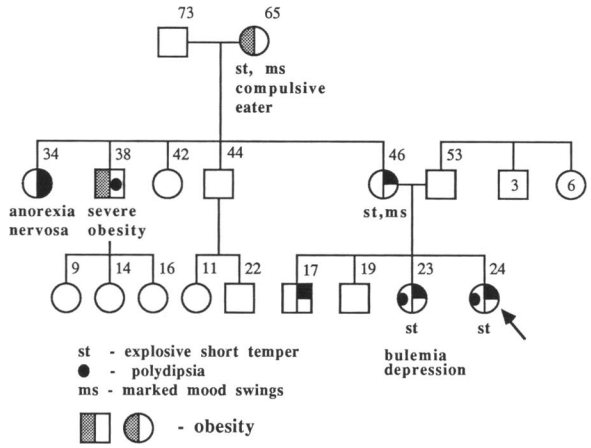

Figure 6

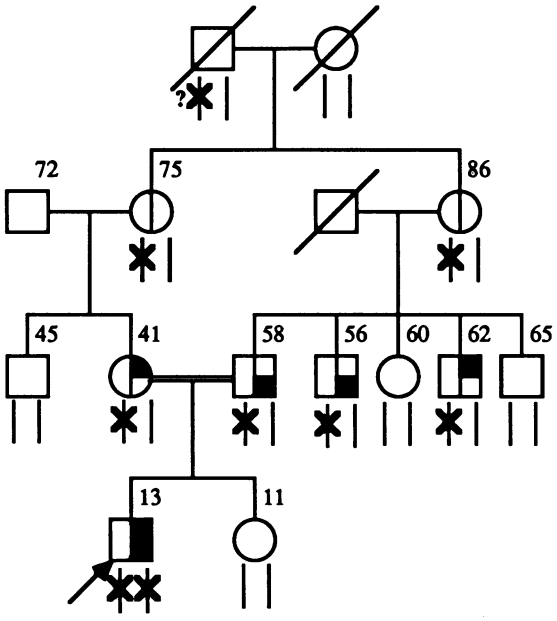

Figure 7

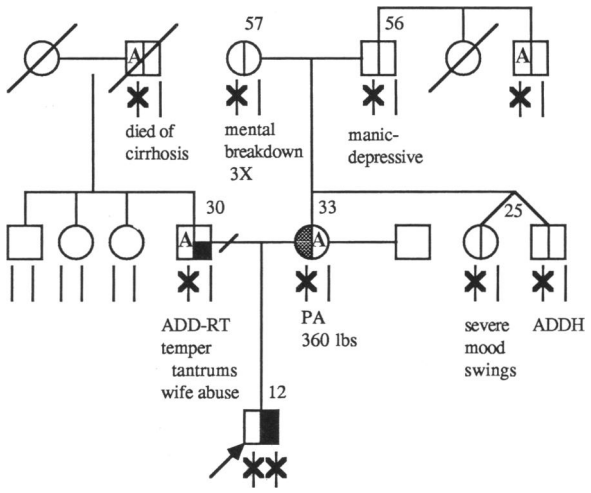

Figure 8

in figure 6, the compulsive behavior can go both ways, to overeating or undereating. In the pedigree shown in figure 6, the sister of the proband had chronic motor tics and bulimia, the uncle had severe obesity, and the aunt had TS and anorexia nervosa.

I suspect that in some cases the gene for TS, for male type II alcoholism, and for the female type of familial obesity are one and the same and that the primary problem is an appetitive compulsion that takes the form of alcoholism in men and of overeating in women. These are not absolutes—the men can also overeat and the women can overdrink. I am also not saying that all type II alcoholics or all obese women carry a *Ts* gene—just that some may.

Some Sample Pedigrees

Figures 7 and 8 show pedigrees that illustrate some of these observations. In these pedigrees the presumptive *Ts* gene carriers are marked with an "X." In figure 7 the 13-year-old boy with TS was the product of a consanguineous marriage. Both parents and two other family members had moderate chronic motor or vocal tics, but none had TS or any of the other, associated behaviors. Not all families do. This is consistent with the proposal that significant TS symptoms represent a homozygous condition and that milder tic symptoms represent the carrier state.

Figure 8 shows a fairly typical TS family. The father has attention-deficit disorder of the residual type, short temper, and alcoholism, and his father died of cirrhosis due to alcoholism. The mother has no motor or vocal tics but has panic attacks and compulsive eating and weighs 360 pounds. Her father was diagnosed as manic depressive, and his brother was alcoholic. Her mother has had several mental breakdowns, her brother had attention-deficit disorder, and her sister had problems with severe mood swings. This pedigree also illustrates the tendency toward obesity in females and toward alcoholism in males. Additional pedigrees are given elsewhere (Comings, submitted).

Genetics versus Psychology

Viewing certain aspects of behavior from a genetic viewpoint results in some striking different conclusions than that suggested by the more classical psychological model. I will give just one of many possible examples. In a recent, popular book, *High Risk Children without a Conscience* by Magid and McKelvey (1987), it was proposed that the psychopathic or antisocial personality was due to separation of the child from its parents at an early age. Figure 9 illustrates the Magid-McKelvey proposal. These authors state that "the chances for increasing numbers of psychopaths are escalating. We must search for answers to the pressing social problems that are helping to create unattached children. We must learn how to prevent unattached children. The solutions will not be easy or cheap, but they must be found" (p. 43).

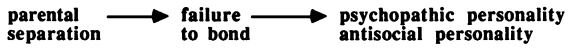

Figure 9

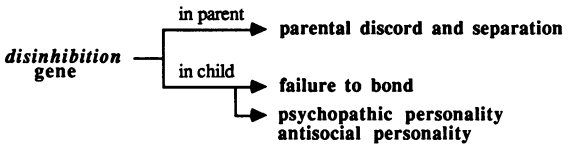

Figure 10

A genetic viewpoint is different and would suggest that a disinhibition-disorder gene carried by a parent could result in marital chaos and separation and that it is this inherited gene—not the fact that the parents separated—that causes antisocial personality in the child. Figure 10 illustrates this concept.

The difference in cost to society of the two approaches can be enormous. With the disrupted-bonding approach, billions of dollars could be spent in social programs that might have no appreciable effect on the incidence of antisocial personality. In the genetic approach, probes to identify the responsible gene in a child with conduct disorder could identify a small number of high-risk individuals who could be appropriately treated at a relatively low cost.

My experience with TS families leads me to suspect that the human brain is actually quite a resistant organ and generally functions well, despite all but the more severe childhood and adult trauma, unless its capacity to function is disrupted by the effects of specific genes.

Geneticists in the Behavioral Sciences

A genetics clinic is a medical clinic that takes care of patients with genetic disorders. This approach includes the whole patient and the whole family. On the basis of our experience with TS, I have observed that caring for many of these individuals from a genetic-biochemical disorder point of view has often rescued them from a mental health–care delivery system that often puts the blame for the illness on the environment, or on the patient, or on the parents, rather than on a biochemical lesion. When the specific chemical lesion is treated, patients often improve, many times dramatically. Patients who have spent years in therapy, being told that the problem is their relationship with their mother, or their toilet training, or their inability to express their anger sometimes show striking improvement in less than a week (Comings, submitted). In fact, compared with treating other genetic disorders, treating this one is rewarding for the physician as well as for the patient.

Freud proposed that many of these disorders were due to an imbalance between the id and the superego and that this imbalance had its origins in problems with object relations in early childhood. I would agree in part but would suggest that the terminology be changed—"id" to "the limbic system" and "superego" to "the prefrontal lobes,"—and that the imbalance between the two is chemical in nature and that the critical event dates to an even earlier time, namely, conception. The problem is not something the parents did to their children but rather something they gave to their children—their genes. This not so subtle distinction can make an enormous difference in approach and treatment.

Because a genetic approach is often so critical, this brings us to the question, What is easier, to teach a geneticist psychology or to teach a psychologist genetics? Both can be difficult tasks, and it almost comes out a draw. However, with the increasing complexity of modern molecular genetics and with the probability that genetic probes will soon be available for a wide range of neurobehavioral syndromes, it is clear that geneticists are going to have to become more familiar with the jargon, the medications, and the intuitions of the behavioral scientists.

However, it is equally true that genetics needs to be part of the curriculum of schools for clinical psychologists. As is true with many of the complexities of modern medicine, a team approach can be part of the solution, but these patients and families need a physician comfortable with genetics and comfortable with medications, and the medical geneticist is well positioned to do this.

If these were just another group of rare disorders, this discussion would be academic. But the sheer number of individuals affected with genetic disorders affecting behavior overwhelms the number of disorders affecting all other organs.

I predict, or at least hope, that within 5 years a significant number of individuals in our human genetics society will become intrigued and involved in this burgeoning field.

Chaos and Genetics

One might also hope that, with knowledge of a few major and a number of minor modifying genes, it would be possible quite accurately to predict certain types of behavior or any other phenotype. However, Charles Sing

recently brought to my attention James Gleick's book *Chaos: Making a New Science* (Gleick 1988). This new science got its start from attempts to develop formulas for long-range weather prediction. We geneticists are used to assuming that, once the molecular genetic basis of a disorder is known, minor changes in input variables produce minor differences in output or phenotype. However, the science of chaos shows that complex systems behave in an unpredictable fashion regardless of how much is known about the variables affecting it.

This is especially relevant for complex systems such as the human brain and the effect of genes on human behavior. It has frequently been assumed that any part of behavior that could not be explained by genetic factors was due to environmental factors. We need to seriously consider the possibility that a significant part of the presumed environmental effect is actually the effect of chaos. With regard to *Ts*-gene carriers, this is illustrated in figure 11.

This is especially relevant to dominant and semidominant disorders. It should also warn us that biochemical changes in these disorders may be rather subtle and yet still have marked effects, and should also warn us that, no matter how much we know about a person's genes and environment, we will never be able to completely predict their behavior.

A new era of understanding behavior at a genetic and molecular level is on us. From my perspective, of all the organs of the human body, in terms of sheer numbers and the greatest impact on society, genetic defects of the brain that affect behavior will be the most important. More than any other area, this brings with it the need for two disciplines to peer into the huge chasm separating them and mentally prepare themselves for the leap—molecular genetics into behavior and behavioral sciences into molecular genetics.

And the public should not be an idle bystander. It is the ultimate irony that, as an understanding of our mind and emotions increases, many lay members of our society withdraw in ignorance or fear into an anti-science, anti-intellectual, and promysticism stance. The public needs to be included in the excitement, for they are the ultimate benefactors of one of man's last frontiers.

Figure 11

Acknowledgments

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